III. Remarks

Claims 1-5 and 12-17 are pending. Claims 1-5 and 12, and 14-15 are currently amended.

Claims 1-5 and 12-17 stand rejected.

Objection to Specification

The Examiner has objected to the specification because it does "not properly cite the application priority date." The specification is currently amended. Applicants believe that as amended the application priority data is properly cited.

Objection to Claims

The Examiner has objected to claims 1-5 and 12-17 "because of the recitation, 'derived' in Claims 1a, 12 and 15" The Examiner suggests replacing "derived" with the term "obtained". Applicants have amended claims 1, 12 and 15 to substitute the word "obtained" with "derived" per the Examiners suggestion.

The Examiner has also objected to claims 2-5 and 16-17 because "at Line one of each one of the cited claims, before the word 'wherein' a--, --should be inserted. Applicants have amended 2-5 and 16-17 accordingly.

With the above amendments, Applicants request withdrawal of the objections.

Objection to Abstract

The Applicants have amended the abstract to correct for an obvious typographical error; the word "patent" was replaced with "patient.

Additional Amendments

For clarity, in the preamble of claims 1 and 15, the phrase "multiple types" has been changed to "a plurality".

Claim 5 has been amended to correct for an obvious typographical error.

Claim Rejections 35 U.S.C. §112 – Second Paragraph

The Examiner has rejected claims 1-5 and 12-17 "because of the recitation of the term "sequence" at line 1 in the preamble of claims 1 and 15 renders these claims unclear. In response, Applicants have amended these claims to replace the phrase "sequence to administer" with the phrase "order of administration."

The Examiner argues that the use of the term "strain" in claims 1, 12 and 15 renders the claims unclear because the art-recognized meaning of this term is "cells having the same genotype or phenotype or both". The Examiner has suggested replacement of this term with the term "clone." In order to address this concern, we instead have amended the claims to remove the term "isogenic." It is therefore clear that a panel of cell strains is provided which has a parental strain and progeny strains. The progeny strains are distinct from each other and thus do not have the same genotype or phenotype as the parental strain.

The Examiner indicates that the term "order" in step c) of claim 1 and claim 15 lacks antecedent basis. Claims 1 and 15 are amended, as above, by replacing the phrase "sequence to administer" with the phrase "order of administration." In light of this amendment Applicants believe that there is sufficient antecedent basis for the word "order" in Claims 1c and 15c.

The Examiner argues that claim 15 is unclear for reciting the term "undesired" in claim 15. We have replaced this term with the term "harmful." Applicants submit that this term is clear and definite and indicates that the cells are being killed in order to reduce the harm to the patient caused by the cells.

Claim Rejections - 35 U.S.C. §103(a)

The Examiner has rejected claims 1 to 5 and 12 to 17 as being obvious over the combined teachings of Alli et al., 2002 and U.S. Patent 6,664,288 to Pardee et al.

The Examiner states that Alli teaches an assay for determining IC_{50} values of chemotherapeutic drugs but does not teach determination of an order of administration of the drugs. The Examiner then relies upon Pardee for the teaching of determining the order of addition of β-lapachone and paclitaxel.

Applicants submit that the combination of the Alli and Pardee references does not disclose all of the features of the claims. Furthermore Applicants submit that the features which are not disclosed in these two references would not have been obvious in light of the general knowledge of one skilled in the art. In particular, this combination of references does not teach the use of panel of cell lines comprising a parental strain sensitive to all of said drugs and two or more progeny strains which

are each resistant to a separate one of said chemotherapeutic drugs as claimed in independent claims 1 and 15.

The Alli reference is directed to an investigation of the effects of stathmin (a protein which plays a role in microtubule dynamics) on the sensitivity to antimicrotubule drugs in human breast cancer (see abstract). A number of different breast cancer cell lines, including BT20, BT474, BT549, MDA-MB-231, MDA-MB-468 and T47D were investigated to determine the extent of expression of stathmin. It was found that the expression levels of stathmin are from 4 to 11 fold greater in this panel of cells relative to the control cell line MCF-10A, which was chosen as the cell line displaying a "baseline" level of stathmin expression (see page 6865, col 2 – Results section). Of this panel of cells, only BT20 cells and BT549 cells were investigated further.

Two clones of BT20 cells were transformed with a vector containing nucleic acid encoding stathmin for the purpose of over-expressing stathmin. These two clones were designated BT20ST1 and BT20ST3. The BT20, BT549, BT20ST1 and BT20ST3 cells were treated with the antimicrotubule drugs paclitaxel and vinblastine and were all found to be less sensitive (i.e. resistant) to both of these drugs (see page 6866, col 2). The BT20ST1 and BT20ST3 cells were then separately treated with the non-antimicrotubule drugs doxorubicin and camptothecin and it was determined that the overexpression of stathmin in these two cell lines did not have an effect on the sensitivity to these drugs (see page 6866, col 2).

In summary, Alli teaches treatment of a number of breast cancer cell lines with antimicrotubule drugs and non-antimicrotubule drugs with the results indicating that BT20, BT549, BT20ST1 and BT20ST2 cells display resistance to both of the antimicrotubule drugs (paclitaxel and vinblastine) but not to the non-antimicrotubule drugs (doxorubicin and camptothecin).

Most notably, it is clear that this reference does not teach the use of a panel of cell lines comprising a parental strain sensitive to all of said drugs and two or more progeny strains which are each resistant to a separate one of said chemotherapeutic drugs as claimed in claims 1 and 15.

In the Alli reference, BT20ST1 and BT20ST3 represent genetically engineered progeny of BT20. However, the parental cell line BT20 and the progeny

cell lines are both resistant to the same drugs (paclitaxel and vinblastine) in contrast to the claimed feature described above.

It is furthermore notable that the aim of the Alli reference is simply to determine the effect of one protein (stathmin) on sensitivity to antimicrotubule drugs. Alli's objective is not commensurate with the claimed subject matter which aims to reduce drug cross resistance in the patient by effectively killing resistant cells.

The Pardee reference is a U.S. Patent directed to a methods and compositions for the treatment of cancer. As pointed out by the Examiner, there is disclosed a method for treating a mammal having a solid tumor by administering β-lapachone (a DNA topoisomerase) and a taxane derivative (a microtubule targeting drug). It is indicated in claim 10 of this patent that Pardee envisions administration of β-lapachone before the addition of the taxane derivative.

Three groups of experiments disclosed by Pardee are based on mouse tumor model systems prepared by innoculation or xenografts of mice with existing human cancer cell lines. The innoculated mice subsequently develop tumors and are treated with β-lapachone, paclitaxel, and a combination thereof (see experiments 1 to 3, cols. 13 to 15. A fourth experiment is based on assays carried out on a group of human cancer cell lines to determine cell death induced by treatment with β-lapachone, paclitaxel, and a combination thereof. In each of these experiments, there is no teaching of investigation of the progeny of any of these cell lines, nor whether the progeny of the cell lines would represent different strains each being resistant to a different drug.

It is indicated in col 16, lines 56 to 58 that the experimental results suggest that the mechanism of the synergistic cancer cell killing effect of the drug combination is dependent upon the order of artificial checkpoint imposition. This means that the enhanced cell-killing activity observed upon treatment with the specified drug combination arises from interference with different points in the cell cycle in a specific order. Pardee thus teaches away from the present claims. Pardee does not teach that the effective cancer cell killing ability of the drug combination is a result of killing certain drug-resistant strains of the cancer cells in a particular order. Pardee furthermore does not determine an order of administration of chemotherapeutic drugs which includes the step of using a panel of cell lines comprising a parental strain sensitive to all of said drugs and two or more progeny

strains which are each resistant to a separate one of said chemotherapeutic drugs as claimed in claims 1 and 15. The lack of this step in the combination of Alli and Pardee indicates that the combination does not render the present claims obvious.

As noted above, there is no teaching in Pardee of progeny strains having drug resistance relative to parental strains. In fact, Pardee does not refer to progeny strains at all. All of the cell lines used by Pardee are previously characterized standard cell lines representing different tumor types and none of these cell lines have been analyzed by Pardee to identify strains within the cell population of the samples used in the investigations. The Examiner's assertion that Pardee intrinsically teaches "least cross resistance of said chemotherapeutic drugs" (page 7 of the Office Action) thus appears to be unfounded.

In view of the foregoing, we respectfully submit that the claims are not obvious in view of Alli and Pardee and request that this rejection be withdrawn.

Conclusion

With this amendment, Applicants believe that all the pending claims are in condition for allowance. Applicants request reconsideration, withdrawal of the objections and rejections, and allowance of the application.

If the Examiner has any questions, the Examiner is respectfully invited to telephone the undersigned attorney.

Respectfully submitted,

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Date

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